REMARKS

Applicant respectfully requests entry of the foregoing amendments prior to continued examination of the application.

I. Claim Amendments

Claim 5 is amended it correct a clerical error. Claim 13 is amended to recite a specific embodiment described, for example, at page 1, paragraph [0002], of the specification as filed. Claims 23 and 26 are amended to correct clerical errors. Upon entry of the amendments, claims 1-3, 5-13, 15-21 and 23-28 will remain pending. These claims are presented for examination.

Applicant reserves the right to pursue any canceled subject matter in one or more applications with the same rights of priority as the instant application.

II. Status of Claims 13-21

Applicant notes with appreciation the indication that claims 13 and 15-21 have been rejoined.

III. Response to Rejections under 35 U.S.C. § 112

Claims 13, 15-21, 23 and 25-28 were rejected for alleged lack of written description. Without acquiescing to the merits of these rejections, Applicant has amended the claim to obviate the Examiner's concerns. For example, claim 13 now recites a method of improving mammographic sensitivity, as taught at page 1 of the application as filed. Additionally, claims 23 and 26 have been amended to recite "hydroxypropylcellulose" instead of "hydroxymethylcellulose." Applicant therefore respectfully requests reconsideration and withdrawal of these rejections.

IV. Response to Rejections under 35 U.S.C. § 103

The Office Action rejects the claims as obvious over Atkinson as evidenced by Boyd and Kolb in view of the Mauvais-Jarvis patent and Mauvais-Jarvis (1986) publication, and further in view of Yamaguchi (U.S. Patent 5,820, 877). Applicant respectfully traverses this rejection.

Atkinson is cited for describing the use of tamoxifen to reduce mammographic breast density; while the Mauvais-Jarvis patent is cited for the general statement that that 4-hydroxy tamoxifen could be administered transdermally to treat benign or cancerous conditions of the breast, and for teaching an aqueous alcoholic gel comprising 4-hydroxy tamoxifen. Yamaguchi is cited for teaching an alcoholic gel formulation comprising a phosphate buffer, ethyl alcohol, isopropyl myristate and hydroxypropylcellulose. This combination of references, however, does not teach or suggest the present invention.

Instant claim 1 is directed to a method of reducing breast density, comprising percutaneously administering, to a patient having class III or class IV dense breast composition, a pharmaceutical composition for percutaneous administration comprising 4-hydroxy tamoxifen and isopropyl myristate. The cited references do not teach or suggest the recited composition, and do not provide a reasonable expectation of the success of the recited method. Thus, the § 103 rejection is improper, and should be withdrawn.

A. No Prima Facie Case of Obviousness

The Examiner cited Yamaguchi as allegedly teaching pharmaceutical compositions comprising isopropyl myristate. Yamaguchi fails to teach or suggest such compositions, however. Yamaguchi does not disclose any formulations comprising isopropyl myristate. While the Office Action cites column 11, lines 21-26, of Yamaguchi, the formulation reported in that example includes myristyl alcohol, not isopropyl myristate. The cited laundry lists of optional components (set forth at column 4, lines 38-42 of Yamaguchi) also does not mention isopropyl myristate. Thus, Yamaguchi does not support the obviousness rejection.

Because the cited references do not even make out a prima facie case of obviousness with respect to the recited composition, the §103 rejection should be withdrawn.

B. No Reasonable Expectation of Success

The obviousness rejection is based in large part on the assumption that it would have been obvious to replace the tamoxifen used by Atkinson with the 4-hydroxy tamoxifen taught in the Mauvais-Jarvis patent because 4-hydroxy tamoxifen is known to be an active

metabolite of tamoxifen, and because 4-hydroxy tamoxifen avoids some side effects associated with tamoxifen. This is an inaccurate reflection of the state of the art, however. As Applicant has explained previously, prior to the present invention there was no knowledge in the art 4-hydroxy tamoxifen would be useful in a method to reduce breast density. Moreover, the reported usefulness of tamoxifen did not provide a reasonable expectation that 4-hydroxy tamoxifen would be useful for reducing breast density.

As further evidence on point, Applicant submits herewith a Declaration under Rule 132 of Dr. Jean Fourcroy. Dr. Fourcroy has a Masters degree in Public Health, an M.D. and Ph.D., and is a consultant for Ascend Therapeutics, Inc., the licensee of the application.

Dr. Fourcroy's testimony evidences that it is not possible to extrapolate from Atkinson's use of tamoxifen to the use of 4-hydroxy tamoxifen described in the application. Fourcroy Declaration, ¶7. As Dr. Fourcroy explains, it is important to understand that tamoxifen and 4-hydroxy tamoxifen are distinct agents, each with unique safety and efficacy profiles. Fourcroy Declaration, ¶7. For example, tamoxifen is dependent upon cytochrome P450 enzymes for metabolism to a more active metabolite, such as 4-hydroxy-tamoxifen, and it is a potent rat liver carcinogen, unlike 4-hydroxy tamoxifen. Fourcroy Declaration, ¶8; Carthew *et al.*, *Archives of Toxicology* 75: 375-80 (2001) (already of record); Sauvez *et al.*, *Carcinogenesis* 20: 843-50 (1999) (already of record).

Each of tamoxifen and 4-hydroxy tamoxifen manifests different and unpredictable biological activities in different cells, determined in part by each compound's individual effect on estrogen receptor conformation. As explained by Dr. Fourcroy, for both tamoxifen and 4-hydroxy tamoxifen, the final response element at the cellular level is dependent on the unique conformation of the estrogen receptor in the individual cell type. Fourcroy Declaration, ¶9; Wijayaratne *et al.*, *Endocrinology* 140: 5828-840 (1999) (submitted herewith); Giambiagi *et al.*, *J. Steroid Biochem.* 30: 213-17 (1988) (already of record). Thus, estrogen receptor binding by tamoxifen recruits different co-factors than estrogen receptor binding by 4-hydroxy tamoxifen. Fourcroy Declaration, ¶9. For example, tamoxifen initiates apoptosis in p53(-) normal human mammary epithelial cells, while 4-hydroxy tamoxifen does not. Fourcroy Declaration, ¶9; Dietze *et al.*, *J. Biological Chemistry* 276: 5384-394 (2001)

(already of record). On the other hand, 4-hydroxy tamoxifen inhibits estrone sulphatase activity in mammary cancer cell lines, while tamoxifen has little effect in this regard. Fourcroy Declaration, ¶9; Chetrite *et al.*, *Anticancer Research* 13: 931-34 (1993) (already of record).

Dr. Fourcroy testifies that the state of the art, as illustrated by the publications cited above, is such that tamoxifen and 4-hydroxy tamoxifen are known to have different modes of action. Thus, according to Dr. Fourcroy, persons versed in this field understand that knowing that tamoxifen is useful in a given therapeutic regimen does not provide a reasonable basis for expecting that 4-hydroxy tamoxifen would be useful for the same purpose. Fourcroy Declaration, ¶10.

Dr. Fourcroy also testifies that the present invention provides significant advantages over the state of the art, particularly over the use of tamoxifen to reduce breast density. Fourcroy Declaration, ¶10. This is because percutaneous 4-hydroxy tamoxifen offers important safety improvements. Fourcroy Declaration, ¶10. While the side effects of tamoxifen were known, it was not known that 4-hydroxy tamoxifen would be useful to reduce breast density. Fourcroy Declaration, ¶10. Thus, the application describes a significant advance in the reduction of breast density. Fourcroy Declaration, ¶10.

The foregoing demonstrates that it was known in the art that tamoxifen and 4-hydroxy tamoxifen are not biologically equivalent and, therefore, are not necessarily interchangeable for therapeutic purposes. In view of this knowledge, those skilled in the art would have had no reasonable expectation of success in using 4-hydroxy tamoxifen in place of the tamoxifen taught by Atkinson. Accordingly, the obviousness rejection is improper and should be withdrawn.

IV. Concluding Remarks

Applicant believes that this application is in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issues remain, the Examiner is invited to contact the undersigned attorney by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extension of time is needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date July 10, 2007

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288